

UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte KENNETH F. BUECHLER,
RICHARD R. ANDERSON,
THEODORE T. LEE, and
GUNARS E. VALKIRS

Appeal No. 2003-2084
Application No. 08/241,061

HEARD: October 7, 2003

WILLIAM F. SMITH, MILLS, and GRIMES, Administrative Patent Judges.

WILLIAM F. SMITH, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 98 through 108. Claims 98 and 99 are representative of the subject matter on appeal and read as follows:

98. A composition of matter comprising:

(a) a plurality of different ligand analogue conjugates, each different ligand analogue conjugate corresponding to one of a plurality of different target ligands, wherein each ligand analogue conjugate comprises a binding site for an antibody or a ligand receptor produced by a standard immunologic technique, and wherein each ligand analogue conjugate is attached via a linkage site to a protein, polypeptide, polymer, or a signal

(b) at least one crosstalk inhibitor comprising an analogue of at least one linkage site present amongst the plurality of different ligand analogue conjugates, wherein the crosstalk inhibitor is present in an amount sufficient to inhibit binding of the linkage site of at least one ligand analogue conjugate in a ligand receptor assay to an antibody or ligand receptor produced by a standard immunologic technique.

(c) a crosstalk inhibitor comprising at least one analogue of the linkage site in an amount sufficient to inhibit binding of the ligand receptor to the linkage site.

Marini et al. (Marini), "A Simple Method for Increasing Hapten Immunogenicity by a Specific Structural Modification of the Carrier," Journal of Immunological Methods, Vol. 120, pp. 57-63 (1989)

Claims 99-102 under 35 U.S.C. § 102(b) as anticipated by Marini; and,

Claims 99-102 under 35 U.S.C. § 102(b) as anticipated by Schuurs.

We reverse all rejections.

Background

The present invention is concerned with a problem in the immunoassay art known as crosstalk. As explained:

Methods to prepare monoclonal antibodies to ligands which, by themselves, do not generate an immunological response are well known to those skilled in the art. The ligand, or an analogue thereof, is generally coupled, chemically, to a carrier molecule, e.g., a protein, peptide, or other polymer, to form an immunogen (one example of a ligand analogue conjugate as defined herein) which elicits an immunological response. Antibodies are thus raised to the surface of the carrier molecule onto which is coupled the ligand. The selection or screening of antibodies is then performed to choose the antibody which best fulfills the intended use of the antibody. The screening of antibodies is well known to those skilled in the art and is generally performed by binding a ligand-carrier conjugate to a solid phase, allowing the raised antibody to bind to the ligand-carrier conjugate and detecting the presence of the bound antibody with a labelled anti-antibody conjugate. An inherent problem with the generation and screening of antibodies is the difficulty in determining the location of binding of the antibody to the ligand, i.e., the binding site; that is, it is not clear which portion of the ligand analogue is bound by the antibody. This can result in the selection of antibodies which possess a very small but definite affinity to the carrier molecule, or to the chemical structure (herein called the "linkage site") which attaches the ligand analogue to carrier molecule. Such an antibody, will thus bind (an occurrence known as crosstalk) to other, or uncomplementary, carrier molecule-ligand complexes having such a linkage, and produce false positive results when such other complexes are present in a test.

Specification, page 6.

The crosstalk problem is addressed by the present invention as follows:

The present invention is directed to ligand receptor assays in which the presence of a multiplicity of ligands are measured in a single determination. In particular, the present invention relates to the preparation and use of reagents as crosstalk inhibitors in ligand receptor assays. The crosstalk inhibitors resemble the chemical structure (or linkage site) which links the ligand analogue to the carrier molecule of a ligand analogue conjugate. Thus, the crosstalk inhibitors reduce or

prevent the crosstalk, i.e., the undesirable interactions between ligand receptors and uncomplementary ligand analogue conjugates.

Specification, page 8.

The crosstalk inhibitors of the present invention are described as follows:

The crosstalk inhibitor, which resembles the linkage chemistry of the ligand analogue conjugates, competes with the linkage chemistry of the ligand analogue conjugates for binding to the terminal solid phase ligand receptor. With the proper crosstalk inhibitor and crosstalk inhibitor concentration, the competition is shifted toward binding of the crosstalk inhibitor and not of the uncomplementary ligand analogue conjugates. The crosstalk inhibitor should compete very poorly with the complementary ligand analogue conjugate for the solid phase ligand receptor because the affinity of the ligand receptor for the complementary ligand analogue conjugate is much higher.

How closely the chemical structure of the crosstalk inhibitor must resemble the linkage chemistry of the ligand analogue depends on the affinity of the ligand receptor for the uncomplementary ligand analogue conjugate. The crosstalk inhibitor may be free in solution or bound to a protein or polymer. When the crosstalk inhibitor is attached to a protein or polymer, it can bind multivalently to the solid phase ligand receptor as can the ligand analogue conjugate. Thus, the multivalent crosstalk inhibitor can better compete with the uncomplementary ligand analogue conjugate than the monovalent crosstalk inhibitor.

Specification, pages 9-10.

As seen from claims 98 and 99, the claimed invention is directed to a composition that comprises a ligand analogue conjugate(s), and a crosstalk inhibitor with or without a ligand receptor. Ligand analogue conjugate is defined as “[a] conjugate of a ligand analogue and a signal development element, a protein, polypeptide, or polymer.” Specification, page 11, lines 14-22.

Discussion

1. Written Description Rejection of Claim 102.

The examiner explains the rejection as follows:

The ligand is 'drug of abuse, metabolite of drug abuse, an analogue of the drug abuse, an analogue of the metabolite of the drug abuse, therapeutic drug, a metabolite of a therapeutic drug, an analogue of a therapeutic drug, and an analogue of a metabolite of a therapeutic drug...' claimed in claim 102 has no clear support in the specification and the claims as originally filed. The subject matter claimed in claims [sic] 102 broadens the scope of the invention as originally disclosed in the specification.

Examiner's Answer, page 4.

Appellants argue that literal support for the language is found in the specification at page 1, line 10 through page 2, line 16 and page 11, lines 9-13. Appeal Brief, pages 28-30. The examiner states that appellants may not rely upon that portion of the specification at page 1 since that portion is "Background of the Invention" and not "drawn to the composition as claimed in the instant claims." Examiner's Answer, page 12.

In reviewing the matter, we find ourselves in agreement with appellants. The examiner is correct in pointing out that the portion of the specification at page 1 which appellants rely upon for written descriptive support of the questioned claim language is headed by the title "Background of the Invention." However the specific text relied upon by appellants uses phrases such as "as used herein" and "in the context of the present invention." Clearly, in describing the "Background of the Invention," appellants are setting forth part of the present invention. In other words, the present invention, as do most inventions, builds upon what was known in the art. The present specification

provides adequate written descriptive support for the language questioned by the examiner.

If the examiner's real concern is that the language set forth in claim 102 does not appear verbatim in the specification, the examiner should require appellants to comply with 37 CFR § 1.75(d)(1) ("The claim or claims must conform to the invention as set forth in the remainder of the specification and the terms and phrases used in the claims must find clear support or antecedent basis in the description so that the meaning of the terms in the claims may be ascertainable by reference to the description.")

The rejection of claim 102 under 35 U.S.C. § 112, first paragraph (written description), is reversed.

2. Written Description Rejection of Claims 98 and 99.

The rejection is explained as follows:

The specification description directed [sic] is directed to specific crosstalk inhibitors which resemble the chemical structure which links the ligand analogue to the carrier, for example the crosstalk inhibitors disclosed in figures 1C to 1F, which clearly do not provide an adequate representation regarding the open ended claimed composition comprising the crosstalk inhibitors, ligand analogue conjugates attached to a protein made of the presently claimed invention.

And moreover, applicants have not shown that they are in possession of a composition which has plurality of different ligand analogue conjugates, each different ligand analogue conjugate has a different linkage site from the linkage of the other ligand analogue conjugates.

Examiner's Answer, page 5.

The examiner relies upon the University of Calif. v. Eli Lilly & Co., 119 F.3d 1559, 1567, 43 USPQ2d 1398, 1405 (Fed. Cir. 1997), stating "[a]lthough directed to DNA compounds, this holding would be deemed to be applicable to any compound; which

requires a representative sample of compounds and/or a showing of sufficient identifying characteristics; to demonstrate possession of the claimed generic(s)."

Examiner's Answer, page 6.

Appellants argue, inter alia:

Moreover, Appellants respectfully submit that the specification as filed clearly indicates to the skilled artisan that Appellants were in possession of the claimed invention at the time of filing. The specification describes the common structural attributes shared by crosstalk inhibitors as defined in the instant specification (i.e., that each is an analogue of a linkage site), as well as common functional attributes shared by crosstalk inhibitors (i.e., that each inhibits crosstalk caused by receptors that recognize the linkage chemistry rather than the ligand). The specification follows this general description of the common structural and functional attributes of crosstalk inhibitors by describing the synthesis of numerous specific crosstalk inhibitors (see, e.g., examples 4-13 and 22). Finally, the specification also describes methods for testing the effectiveness of crosstalk inhibitors in ligand-receptor assays (see, e.g., example 30).

Appeal Brief, paragraph bridging pages 39-40. In response, the examiner states:

Appellants [sic] arguments regarding the possession of the claimed composition at the time of filing have been considered, but are not persuasive. Appellants argue that the instant claimed composition comprise a mixture of ligand analogue conjugates, cross talk inhibitors and ligand receptors. It is noted that claim 98 composition does not have the ligand receptor as in appellants [sic] argument. Appellants assert that the specification describes the common structural attributes shared by cross talk [sic] inhibitors as defined, as well as common functional attributes shared by cross talk [sic] inhibitors. Appellants [sic] assertions have been considered but are not persuasive. The narrow scope of examples directed to **specific crosstalk inhibitors** are clearly not representative of the scope of the presently claimed composition.

Examiner's Answer, page 13, 2nd paragraph (emphasis in original).

In considering the matter, we find ourselves in agreement with appellants' position again. Appellants have carefully explained how the specification reasonably describes a genus of crosstalk inhibitors. The examiner has focused upon the so-called "open ended claimed composition" (Examiner's Answer, page 5) and "narrow scope of

examples directed to **specific crosstalk inhibitors**" (Examiner's Answer, page 13)(emphasis in original). Merely pointing to the breadth of a claim limitation does not establish that that claim limitation does not enjoy written descriptive support as required by 35 U.S.C. § 112, first paragraph. On this record, we do not find that the examiner has established a prima facie case of lack of written description for claims 98 and 99.

The rejection under 35 U.S.C. § 112, first paragraph (written description) of claims 98 and 99 is reversed.

3. Enablement Rejection of Claims 98-102.

The examiner considers the specification to be enabling for compositions "comprising specific crosstalk Inhibitors (as in figures 1C-1F) and ligand conjugate, [sic]" but not for "any composition comprising ligand analogue conjugate and any crosstalk inhibitors." Examiner's Answer, page 6. In support of the rejection, the examiner provides an analysis of the factors set forth in In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), i.e., (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

We first point out that application 07/683,456 is stated to be a parent application of this application. U.S. Patent No. 5,525,524 ('524 patent) also traces its parentage to application 07/683,456. In response to an obviousness-type double patenting rejection based upon the claims of the '524 patent, appellants have filed a terminal disclaimer. Paper No. 43, April 23, 1999. Claim 3 of the '524 patent reads as follows:

3. A method for identifying a crosstalk inhibitor for a ligand analogue conjugate, wherein said ligand analogue conjugate comprises a binding site attached via a linkage site to a protein, polypeptide or label, and wherein said crosstalk inhibitor competes with said linkage site for binding to a ligand receptor, wherein said ligand receptor is an antibody which binds said linkage site, said method comprising the steps of:

(a) making a potential crosstalk inhibitor comprising at least one analogue of a linkage site of a ligand analogue conjugate,

(b) testing said potential crosstalk inhibitor by:

(i) performing a first assay utilizing a first reaction mixture comprising said ligand analogue conjugate and a ligand receptor, wherein said ligand receptor binds said linkage site causing a false positive result;

(ii) performing a second assay utilizing a second reaction mixture comprising said ligand analogue conjugate, said potential crosstalk inhibitor and said ligand receptor;

(iii) comparing the results of said first assay and said second assay, so that no false positive result or a reduced false positive result in said second assay indicates that said potential crosstalk inhibitor is useful crosstalk inhibitor.

As seen from claim 3 of the '524 patent, the USPTO has already determined that a method for identifying crosstalk inhibitors of the present invention is patentable subject matter. The present enablement rejection questions whether one skilled in the art would be able to identify crosstalk inhibitors without undue experimentation. It appears that the USPTO has already answered that question in the affirmative by issuing claim 3 of the '524 patent.

Furthermore, the examiner's analysis does not take into account the starting point of a crosstalk inhibitor, i.e., knowledge of the linkage site which is part of the ligand analogue conjugate. Development of a crosstalk inhibitor of the present invention does not begin in a vacuum. Rather, the skilled artisan must start with

knowledge of the linkage site of the ligand analogue conjugate in order to develop analogues to the linkage site to evaluate as possible crosstalk inhibitors.

The examiner's evaluation of the Wands factors overemphasizes the examiner's view of the breadth of the claims and does not take into account that the USPTO has allowed claim 3 of the '524 patent as well as the fact that the starting point of the present invention includes knowledge of the linkage site of the ligand analogue conjugate.

The rejection of claims 98-102 under 35 U.S.C. § 112, first paragraph (enablement), is reversed.

4. Rejection of claims 98-108 Under 35 U.S.C. § 112, second paragraph.

The examiner has set forth six reasons why the claims on appeal are indefinite on pages 9-10 of the Examiner's Answer. Included are questioning of the phrase "corresponding to" as it appears in claims 98-108 and the phrase "standard immunological technique" as it appears in claim 98.¹ However, the examiner states at page 3 of the Examiner's Answer, "[t]he rejection of claims 103-108 'corresponding to'; and the rejection of claim 99 'standard immunological technique' under 35 U.S.C. 112, second paragraph as indefinite has been withdrawn." Presumably the examiner withdrew the rejection of claim 99 in regard to the phrase "standard immunological technique" because the language does not appear in the claim. As the record stands, the examiner on one hand withdraws the rejection in this regard and on the other hand maintains the rejection. Given the examiner's positive statement that the rejection has

¹ The examiner states at page 9 of the answer that claim 99 also contains this language. However, the record copy of claim 99 (Paper No. 50) does not contain the phrase "standard immunological technique."

been withdrawn as to these two claim limitations, we conclude that the continued maintenance of this aspect of the rejection is an oversight on the part of the examiner.

We will also reverse the remainder of the rejection. The examiner first questions the phrase "ligand analogue conjugate" as used in claims 98-108 stating "[i]t is not clear what does [sic] applicants mean by analogue." However, as set forth above, the specification provides an explicit definition of "ligand analogue conjugate." Furthermore, this aspect of the rejection is contrary to the issuance of the '524 patent by the USPTO since claims of that patent are also directed to ligand analogue conjugates.

The examiner next questions the phrase "analogue of linkage site" as used in claims 98-99, stating "[t]he specification no where teaches what are the analogues of the linkage site. And the specification no where teaches how are the analogues in the linkage site can be [sic] prepared." Examiner's Answer, page 9. The specific questions raised by the examiner in regard to this claim language appear to be more directed to enablement rather than exploring the metes and bounds of the claim language. The examiner has not established that one skilled in the art would have any difficulty in determining whether a given compound would be considered an "analogue of the linkage site" as this phrase is used in claims 98 and 99. Again, this aspect of the rejection is in conflict with the issuance of the '524 patent by the USPTO since the phrase "analogue of the linkage site" is used in claim 3 of the '524 patent.

The next aspect of the rejection is the use of the phrase "standard immunological technique" in claim 98 with the examiner stating: "it is not clear what does [sic] applicants mean by 'standard immunological techniques[']. Does applicant [sic] mean

that the analogue is produced by the standard immunological techniques, it is not clear what are the the standard immunological techniques. The specification no where teaches the 'standard immunological techniques['] useful in the claimed invention." Examiner's Answer, pages 9-10.

Appellants respond that the phrase refers to ligand receptors and "one of skill in the art would understand that ligand receptors produced by 'standard immunological techniques' refers to methods or techniques used to prepare antibodies, or other ligand receptors that are fragments of antibodies, and that retain the binding specificity of the antibody (e.g., an Fab fragment, Fab' fragment, etc.)." Appeal Brief, page 26.

In response to this argument, the examiner states "it is not clear what are the standard immunological techniques used to prepare the ligand receptor." Examiner's Answer, page 18. From the statement of the rejection and the response to appellants' arguments it is apparent that the examiner has not used the correct legal standard in making the rejection. "[T]he definiteness of the language employed [in a claim] must be analyzed--not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art." In re Moore, 439 F.2d 1232, 1235, 169 USPQ 236, 238 (CCPA 1971)(footnote omitted). Here the examiner has considered the referenced term in a vacuum. There is no analysis of the prior art or the application disclosure. On this record, the examiner has not established a prima facie case of indefiniteness.

The examiner next questions the language found in claims 98-99 "in an amount sufficient to inhibit binding of the linkage siteof at least one ligand conjugate to an

antibody or receptor" The examiner states that it is "not clear which amount would be sufficient to inhibit binding of the linkage site to the receptor. The specification nowhere teaches the amount necessary for the inhibition of binding of the linkage site. Applicants are requested to include the amount of inhibitors required." Examiner's Answer, page 10.

The examiner's request for appellants to "include the amount of inhibitors" in the claims is unreasonable. As explained in In re Mattison, 509 F.2d 563, 184 USPQ 484 (CCPA 1975), it is proper for a patent applicant to define their invention through use of functional amounts provided the specification sets forth sufficient guidance so that one skilled in the art would be able to determine an appropriate amount. Here, the examiner has focused on the lack of numerical limitations in the claims and has not analyzed the specification of this application and explained why there is insufficient guidance that would allow one to arrive at an appropriate amount.

Finally, the examiner rejects claim 102 for reciting "drug of abuse, metabolite of drug abuse, and analogue of the drug abuse . . . and an analogue of a metabolite of a therapeutic drug." The examiner merely states that "the specification does not recite that the ligand can be either of those. The specification defines the ligand is a binding partner of a receptor." As set forth above in regard to the examiner's rejection of claim 102 under 35 U.S.C. § 112, first paragraph (written description), we find that the specification of this application does describe these compounds as being the ligand of interest in the present invention.

The examiner's rejection under 35 U.S.C. § 112, second paragraph, is reversed.

5. Rejection of Claims 98-102 as Anticipated by Kinoshita.

The examiner rejects these claims stating "Kinoshita et al teach immunoassay for captopril comprising a plurality of molecules of captopril-MCC-beta-galactosidase (refers to the ligand analogue conjugate of the instant claims) and maercaptoethanol[sic]-MCC (refers to crosstalk inhibitors of the instant claims). Thus, the reference clearly anticipates the claimed invention." Examiner's Answer, page 10.

With regard to claim 98, appellants point out that this claim requires that the composition comprise a "plurality of different ligand analogue conjugates." Appeal Brief, page 13. The examiner has not pointed out where Kinoshita describes a composition which comprises a plurality of different ligand analogue conjugates. Thus, we reverse the rejection as it pertains to claim 98.

We also reverse the rejection as it pertains to claims 99-102. Claims 99-102 require a composition which comprises a defined ligand analogue conjugate, ligand receptor, and crosstalk inhibitor. The examiner's statement of the rejection takes into account only the ligand analogue conjugate and crosstalk inhibitor. Nowhere does the statement of the rejection take into account the ligand receptor. Thus, even assuming arguendo the examiner correctly correlated the stated compounds of Kinoshita to the ligand analogue conjugate and crosstalk inhibitor in claims 99-102, the statement of the rejection does not take into account the subject matter of any claim as a whole.

Furthermore, the examiner has merely pointed to two compounds described in the reference. The claimed invention is directed to a composition which contains three specified compounds. The examiner has not pointed to any composition described in Kinoshita which comprises compounds which meet the requirements of the claims 99-102.

The examiner's rejection of claims 98-102 under 35 U.S.C. § 102(b) based upon Kinoshita is reversed.

6. Rejection of claims 99-102 as anticipated by Marini.

The reasons given by the examiner in regard to this rejection are that:

Marini et al teach a simple procedure to bind to haptens, drugs, peptides (refers to ligand analogues of the instant claims) selectively through their amino or carboxyl group to a spacer (refers to linkage site of the instant claims). The reference specifically teach conjugation of chemical spacers to acetylated gelatin (refers to crosstalk inhibitor comprising analogue of the linkage site). The reference anticipates the claimed invention.

Examiner's Answer, page 11. Again, the examiner has not taken into account that claims 99-102 require three components. The examiner has not pointed to any specific composition described in Marini which comprises the three components required by claims 99-102 on appeal.

The examiner's rejection of claims 99-102 as anticipated by Marini is reversed.

7. Rejection of claims 99-102 as anticipated by Schuurs.

The examiner's statement of the rejection reads as follows: "Schuurs et al. teach immuno assay composition comprising, ligand analogue conjugate (estroidal-17-succinyl-HRP), a cross talk inhibitor (estroil which has analogue of the linkage site). The reference clearly anticipates the claimed invention." Examiner's Answer, page 11. Once again, the examiner has not taken into account that the compositions of claims 99-102 must have three components not two and has not pointed to any specific composition described in Schuurs which comprises the three components required by claims 99-102.

The examiner's rejection of claims 99-102 under 35 U.S.C. § 102(b) as anticipated by Schuurs is reversed.

The decision of the examiner is reversed.

REVERSED

William F. Smith
Administrative Patent Judge

Demetra J. Mills
Administrative Patent Judge

Eric Grimes
Administrative Patent Judge

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